1048,104

PATENT SPECIFICATION

NO DRAWINGS

1,048,104

Date of Application and filing Complete Specification: Feb. 7, 1964.

No. 5292/64.

Application made in United States of America (No. 262,366) on March 4, 1963

Complete Specification Published: Nov. 9, 1966.

Index at acceptance:—A5 B(1C, 1D, 1H, 1N, 1R2, 1S, 1V2, 1Z, 2C, 2D, 2H, 2N, 2R2, 2S, 2V2, 2Z, 3, 6); C2 C(2B43A4, 2B43B4, 3A10A4G, 3A10A5A1, 3A10A5E, 3A10A5K, 3A10E3D1, 3A10E5E, 3A19A1, 3A19B2, 3A19C1, 3A19D2)

Int. Cl.:—A 61 k 3/00 // C 07 c, d

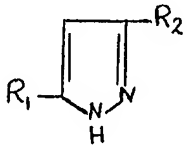
COMPLETE SPECIFICATION

Pharmaceutical Compositions containing 3,5-Disubstituted Pyrazoles

We, THE UPJOHN COMPANY, a corporation organized and existing under the laws of the State of Delaware, United States of America, of 301, Henrietta Street, Kalamazoo, State of Michigan, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to hypoglycemic compositions containing certain 3,5-disubstituted pyrazoles.

The essential active ingredients utilized in the novel compositions and method of this invention are represented by the formula



wherein R_1 is alkyl and R_2 is carboxyl, alkoxycarbonyl, carbamoyl and alkyl-monosubstituted carbamoyl, the said alkyl groups containing 1 to 4 carbon atoms, and physiologically acceptable salts thereof, including alkali metal salts (such as sodium and potassium), alkaline earth metal salts (such as aluminum, calcium and magnesium), ammonium salts and amine salts (such as N,N'-dibenzylethylenediamine, procaine and diethanolamine).

These compounds have been unexpectedly found to exhibit many times the oral hypoglycemic activity of tolbutamide in standard test animals. This pronounced activity is accompanied by a low order of toxicity, making pharmaceutical compositions comprising such compounds dispersed in a solid vehicle or in a liquid which is a non-solvent for the compounds useful in reducing the blood sugar content of mammals, and in particular for administration by the preferred oral route in the management of human diabetes. These compositions are also useful in treating ketosis in children and in the management of hypercholesteremia by reducing blood and tissue levels of cholesterol.

In utilizing the compositions the exact schedule of administration in humans and animals is determined individually according to the subject's age, weight, response to the medication and nature and severity of the condition being treated. For use in reducing the blood sugar content of humans, for example, from 2.5 to 200 mg. of 3,5-disubstituted pyrazole can be administered orally as a composition in unit dosage form one to four times daily, single adult oral dosage forms containing 10 to 150 mg. of the said agent being preferred.

In addition to 3,5-disubstituted pyrazoles as the sole active ingredient, other complementary active ingredients can be included in the composition to secure advantageous combinations of properties especially adapted to individual situations in the treatment of the foregoing conditions. Thus, other hypoglycemic agents such as tolbutamide, chlorpropamide, phenformin hydrochloride, mesoxalic acid, insulin or nicotinic acid, can be included in the present formulations in amounts not exceeding and preferably less than those normally employed in single unit doses where such added ingredients are employed alone. Utilizable potassium salts, such as potassium chloride, can be included to offset possible potassium losses during therapy.

Such admixtures include also conventional therapeutic amounts or less of other hypocholesteremic agents, such as the D-isomer of

3,5,3'-triiodothyronine, triiodothyropropionic acid, and thyroxine-like compounds such as sodium L-thyroxine and sodium D-thyroxine; glucocorticoids such as hydrocortisone, prednisolone and 6α-methylprednisolone; anticoagulants such as heparin, 2-diphenylacetyl-1,3-indandione; polyethylene sulphonate and dicoumarol or its derivatives; vitamins such as nicotinic acid, vitamin B_{12}, ascorbic acid and pyridoxine hydrochloride; estrogens such as estradiol; androgens such as testosterone; combinations of estrogens and androgens such as estradiol together with testosterone; antibiotics such as neomycin; analgesics such as aspirin; compounds associated with cholesterol synthesis or metabolism such as α-phenylbutyric acid and α-p-biphenylbutyric acid; lipotropic agents such as choline and inositol; amino acids such as taurine and glycine; sterols such as sitosterol and other plant sterols; diuretics such as ethoxazolamide and hydrochlorothiazide; anorexigenic agents such as amphetamine; cardiovascular agents (including vasodilators and hypotensive agents), such as chlorisodamine chloride, hexamethonium chloride, and pentaerythritol tetranitrate.

In adapting the active ingredients for use in mammals, including humans, the novel compositions are suitably presented for administration in unit dosage form as tablets, pills, capsules, powders, wafers, cachets, granules, and oral or parenteral aqueous dispersions, including elixirs.

For preparing solid compositions such as tablets, the active ingredient is mixed with a conventional non-sugar tableting component such as cornstarch, dicalcium phosphate, terra alba (calcium sulphate), talc, stearic acid, calcium stearate, gums, and functionally similar materials constituting pharmaceutical diluents or carriers. The tablets or pills can be laminated or otherwise compounded to provide a dosage form affording the advantage of prolonged or delayed action or of predetermined successive action of the enclosed medication. For example, the tablet or pill can comprise an inner dosage and outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids or mixtures of polymeric acids with such materials as shellac, shellac with cetyl alcohol, or cellulose acetate phthalate. A particularly advantageous sustained release coating comprises a styrene-maleic acid copolymer.

The liquid forms in which the novel compositions of this invention can be incorporated include aqueous sugar-free dispersions or suspensions, as well as elixirs and similar pharmaceutical vehicles while excluding from the scope of the invention simple dispersions in water only. Suitable dispersing or suspending agents for aqueous suspensions include the synthetic and natural gums such as tragacanth, acacia, dextran, methylcellulose, polyvinylpyrrolidone and gelatin.

The 3,5-disubstituted pyrazoles as hereinbefore defined are prepared by methods well established in the art, as representatively illustrated in the examples below.

The specification for the novel unit dosage forms of this invention are dictated by and directly dependent on (a) the unique characteristics of the active material and the particular therapeutic effect to be achieved and (b) the limitations inherent in the art of compounding such an active material for therapeutic use in humans, as disclosed in detail in this specification, these being features of the present invention. Examples of suitable unit dosage forms, as heretofore described, are tablets, capsules, pills, powder packets, wafers, cachets, granules, non-aqueous solutions or suspensions for oral or sterile injectable use or suppositories.

Testing of the antidiabetic compounds herein was conducted by a method in which tolbutamide, employed at a minimum effective dose of 25 mg./kg., was administered orally to glucose-primed, fasted (18—24 hours), intact male rats. The test compound was administered orally at a dosage of 200 mg./kg. in 0.5 ml. of an aqueous 0.5% w/v sodium carboxymethylcellulose vehicle. Immediately prior to giving the test material the animals were injected subcutaneously with 100 mg. of glucose. The rats were bled two hours later via the *vena cava* and blood sugars determined. A significant depression of blood sugar from that of 6 vehicle controls was taken to indicate activity.

The hypoglycemic activity of representative compounds herein, as determined by the foregoing test procedure, are shown in the following table:

Compound	Potency × tolbutamide
3-carboxy-5-methylpyrazole	200
3-carboxy-5-ethylpyrazole	10—15
3-ethoxycarbonyl-5-methylpyrazole	50
3-carbamoyl-5-methylpyrazole	25
3-methylcarbamoyl-5-methylpyrazole	8—10

The following examples illustrate the best mode contemplated for carrying out the invention, but these examples are not to be construed as limiting the scope thereof.

Example 1 3-Carboxy-5-methylpyrazole.

To a solution of 3.9 gm. (0.03 mole) of acetopyruvic acid in 30 ml. of water was added 3.9 gm. (0.03 mole) of hydrazine sulphate in 30 ml. of water. The reaction mixture was stirred at 50° C. for ½-hour, cooled and filtered to obtain 2 gm. of product which melted at 240.5—241.5° C. This material was recrystallized from an isopropanol-ethanol solution to give 1.2 gm. (32%) of 3-carboxy-5-methylpyrazole which melted at 243.5—245° C. (Lit m.p. 236—236.5° C.).

Anal. Calcd. for $C_5H_6N_2O_2$: C, 47.62; H, 4.80; N, 22.22
Found: C, 47.51; H, 4.24; N, 21.95

Infrared and NMR spectra support the structure.

A lot of 10,000 compressed tablets, each containing 10 mg. of 3-carboxy-5-methylpyrazole, is prepared from the following ingredients:

3-carboxy-5-methylpyrazole	100 gm.
Terra alba (calcium sulfate)	2500 gm.
Methylcellulose, USP (15 cps.)	65 gm.
Talc, bolted	450 gm.
Calcium stearate, fine powder	35 gm.

The 3-carboxy-5-methylpyrazole and terra alba are mixed well, granulated with 7.5% solution of methylcellulose in water, passed through a No. 8 screen and dried at 120° F. The dried granules are passed through a No. 12 screen, mixed thoroughly with the talc and stearate and compressed into tablets.

One tablet is given three times daily in the oral treatment of diabetes in adult humans.

Example 2 Injectable preparation.

An injectable preparation is made from the following ingredients to contain 150 mg. of 3-carboxy-5-methylpyrazole per ml.

3-carboxy-5-methylpyrazole	15.0%
Sodium carboxymethylcellulose (low viscosity)	0.5% (w/v)
Tween 80—Registered Trade Mark—(polyoxyethylene sorbitan monooleate)	0.4%
Sodium chloride	0.9%
Benzyl alcohol	0.9%
Sterile distilled water, q.s.	100.0 ml.

The previously sterilized active ingredient is homogenized with the already mixed and sterilized vehicle.

Administration is on a basis of 1 ml. daily given intramuscularly in the management of adult human diabetes.

Six thousand units of insulin can be added to the above formulation to give a combination product administrable in 0.5 ml. amounts or less daily.

Example 3 3-carboxy-5-ethylpyrazole.

Sodium metal, 5.65 gm. (0.235 mole), was dissolved in 115 ml. of absolute ethanol. A solution of 31 ml. (0.225 mole) of ethyl oxalate in 20.5 ml. (0.225 mole) of methylethylketone was added to the solution of sodium ethoxide with rapid stirring, keeping the temperature at 15° C. The solution was stirred for several hours, allowed to stand overnight at room temperature under nitrogen, and concentrated under vacuum to a dark viscous oil (sodium ethylpropiopyruvate).

The crude sodium ethylpropiopyruvate and 18.4 gm. of sodium acetate were dissolved in 225 ml. of water. Solid hydrazine sulphate was then added slowly to the aqueous solution while keeping the temperature below 30° C. The mixture was stirred at room temperature for several hours, allowed to stand at room temperature overnight, and extracted with ether, washed with a saturated sodium chloride solution, dried and concentrated under vacuum. There was obtained about 35 gm. of a dark oil (3-ethoxycarbonyl-5-ethylpyrazole).

To a solution of 35 gm. of 3-ethoxycarbonyl-5-ethylpyrazole in 210 ml. of acetone and 210 ml. of water was added 84 ml. of 2.59 N sodium hydroxide. This solution was stirred at room temperature overnight, and 70.5 ml. of 3.1 N hydrochloric acid was then added. The solution was concentrated under vacuum until an oil layer formed. The mixture was extracted with ether, washed with saturated sodium chloride solution, dried and concentrated under vacuum. The residue was recrystallized from 200 ml. of hot water and treated with activated charcoal to give 3.5 gm. of 3-carboxy-5-ethylpyrazole, which melted at 189—192.5° C.

Anal. Calcd. for $C_6H_8N_2O_2$: C, 51.42; H, 5.75; N, 19.99
Found: C, 51.79; H, 5.98; N, 19.84.

Infrared spectra supports the structure.

Substitution of 3-carboxy-5-ethylpyrazole or the corresponding 5-propyl or 5-butyl derivatives for the 3-carboxy-5-methylpyrazole in the pharmaceutical formulation of Example 1 gives tablets useful in the same manner as described therein.

Example 4 3-carboxy-5-methylpyrazole, sodium salt.

To an aqueous suspension of 3-carboxy-5-methylpyrazole in water is added one equivalent of sodium carbonate and the mixture stirred at room temperature for 3 hours. The mixture is filtered and the solution concentrated in a steam bath under reduced pressure to give the sodium salt of 3-carboxy-5-methylpyrazole. This sodium salt can be substituted for the 3-carboxy-5-methylpyrazole in the pharmaceutical formulation of Example 1.

Other alkali metal salts (such as the potassium salt), alkaline earth metal salts (such as aluminum, calcium or magnesium salts), ammonium salts, or amine salts (such as N,N'-dibenzylethylenediamine, procaine and diethanolamine) can be substituted for the sodium salt above.

Example 5 3-ethoxycarbonyl-5-methylpyrazole

To a 5-l. flask with an efficient stirrer was charged 75 gm. (3.27 moles) of sodium metal. Then 2 l. of absolute ethanol was slowly added so as to maintain a moderate reflux. After the sodium had completely dissolved the solution was cooled to room temperature and a solution of 440 gm. (3.0 moles) of ethyl oxalate and 174 gm. (3.0 moles) of acetone was added slowly over a 2½-hour period. The reaction became very thick. The reaction was allowed to stir overnight and was then centrifuged and decanted. The yellow-brown solid was dried and stored under vacuum to give 450 gm. (83%) of sodium ethyl acetopyruvate.

To a solution of 19.7 gm. (0.15 mole) of hydrazine sulphate and 12.4 gm. (0.15 equiv.) of sodium acetate in 150 ml. of water was added 27.3 gm. (0.15 mole) of sodium ethyl acetopyruvate. The temperature rose to 45° C., and the pH of the solution was 5. The dark solution was stirred overnight, cooled and filtered. The solid was recrystallized from Skellysolve B (hexane hydrocarbons) to give 13 gm. (57%) of 3-ethoxycarbonyl-5-methylpyrazole, which melted at 84—86° C.

Anal. Calcd. for $C_7H_{10}N_2O_2$: C, 54.53; H, 6.54; N, 18.17.
Found: C, 54.35; H, 6.30; N, 17.73.

Infrared spectrum supports the structure.

A lot of 10,000 two-piece hard gelatin capsules for oral use, each containing 50 mg. of 3-ethoxycarbonyl-5-methylpyrazole, is prepared from the following materials:

3-ethoxycarbonyl-5-methylpyrazole	500 gm.
Potassium chloride	4000 gm.
Mineral oil, USP	129.6 gm.
Magnesium stearate, powder	162 gm.
Talc, USP	162 gm.
Corn starch	1616 gm.

The powdered 3-ethoxycarbonyl-5-methylpyrazole is mixed thoroughly with the rest of the powdered ingredients and then encapsulated.

One capsule daily is given in the treatment of human diabetes.

Other 3-alkoxycarbonyl-5-alkylpyrazoles, in which the alkyl groups contain 1 to 4 carbon atoms, can be substituted for the 3-ethoxycarbonyl-5-methylpyrazole above.

Example 6 3-carbamoyl-5-methylpyrazole.

A solution of 6.1 gm. (0.04 mole) of 3-ethoxycarbonyl-5-methylpyrazole in 30 ml. of concentrated ammonium hydroxide was heated on the steam bath for 1 hour. The solution was cooled and filtered. The solid was washed with water and dried to give 2.2 gm. of material which melted at 166—168° C. This material was recrystallized twice from water and once from ammonium hydroxide to give 1.1 gm. (22%) of 3-carbamoyl-5-methylpyrazole, which melted at 171—174.5° C.

Anal. Calcd. for $C_5H_7N_3O$: C, 47.99; H, 5.64; N, 33.58.
Found: C, 48.32; H, 5.33; N, 32.86.

Infrared spectrum supports the structure.

A batch of 1000 soft gelatin capsules, each containing 2.5 mg. of 3-carbamoyl-5-methylpyrazole in mineral oil, is prepared from the following materials:

3-carbamoyl-5-methylpyrazole	2.5 gm
Mineral oil, USP	10 gm.

A uniform dispersion of the active ingredient in the mineral oil is prepared and the dispersion filled into soft gelatin capsules by conventional means.

One capsule is given three times a day in the treatment of diabetes in humans.

Other 3 - carbamoyl - 5 - alkylpyrazoles, in which the alkyl group is ethyl, propyl or butyl, can be substituted for the 3-carbamoyl-5-methylpyrazole above.

Example 7 3-N-methylcarbamoyl-5-methylpyrazole.

A mixture of 12.6 gm. (0.1 mole) of 3-carboxy-5-methylpyrazole in 20 ml. of thionyl chloride was heated on the steam bath overnight. The excess thionyl chloride was distilled off and the solid residue was slurried with ether and filtered. The yellow solid was then slurried in hot benzene, water, isopropanol and ether. There was obtained after drying 10.5 gm. (97%) of yellow, insoluble 3 - carboxy - 5 - methylpyrazole dimer, which melted above 270° C. (Lit. m.p. >340° C.).

Infrared spectrum supports the structure.

To a solution of 5.0 gm. (0.065 mole) of a 40% aqueous solution of methylamine in 6 ml. of water was added 5.0 gm. (0.023 mole) of the dimer of 3-carboxy-5-methylpyrazole. The mixture was stirred for ½-hour, cooled and filtered. The solid was dissolved in methanol, treated with activated charcoal and filtered. The filtrate was concentrated to dryness to give 5 gm. of material which melted at 152—160° C. This material was suspended in absolute ethanol, filtered and concentrated to a small volume and cooled. The crystals were filtered and washed with Skellysolve B to give 3.2 gm. of 3-N-methylcarbamoyl-5-methylpyrazole which melted at 163—168° C.

Anal. Calcd. for $C_6H_9H_3O$: C, 51.78; H, 6.52; N, 30.20.
Found: C, 51.57; H, 6.64; N, 29.65.

Infrared spectrum supports the structure.

An aqueous oral suspension containing, in each 5 ml., 200 mg. of 3-N-methylcarbamoyl-5-methylpyrazole, is prepared from the following materials:

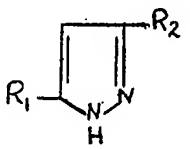
3-N-methylcarbamoyl-5-methylpyrazole	400 gm.
Methylparaben, USP	7.5 gm.
Propylparaben, USP	2.5 gm.
Saccharin sodium	12.5 gm.
Cyclamate sodium	2.5 gm.
Glycerin	3000 ml.
Tragacanth powder	100 gm.
Orange oil flavor	10 gm.
F. D. and C. orange dye	7.5 gm.
Deionized water, q.s.	10,000 ml.

One teaspoonful (5 ml.) daily is employed in the treatment of human diabetes.

Substitution of other 3-N-alkylcarbamoyl-5-alkylpyrazoles, where the alkyl groups contain 1 to 4 carbon atoms, for the above active ingredient gives similarly useful compositions.

WHAT WE CLAIM IS:—

1. A therapeutic composition comprising: as the essential active ingredient, (1) a 3,5-disubstituted pyrazole of the formula:



wherein R_1 is alkyl and R_2 is carboxyl, alkoxycarbonyl, carbamoyl or alkyl-monosubstituted carbamoyl, said alkyl groups containing 1 to 4 carbon atoms, or (2) a physiologically acceptable salt thereof, dispersed in a solid vehicle or in a liquid which is a non-solvent for the active ingredient.

2. A therapeutic composition as claimed in claim 1 and in a unit dosage form containing from 2.5 to 200 mg. of a 3-carboxy-5-alkylpyrazole, said alkyl group containing 1 to 4 carbon atoms.

3. A therapeutic composition as claimed in claim 1 and in a unit dosage form containing from 10 to 150 mg. of 3-carboxy-5-methylpyrazole.

4. A therapeutic composition as claimed in claim 1 and in a unit dosage form containing

from 10 to 150 mg. of 3-carboxy-5-ethylpyrazole.

5. A therapeutic composition as claimed in claim 1 and in a unit dosage form containing from 2.5 to 200 mg. of a 3-alkoxycarbonyl-5-alkylpyrazole; said alkyl groups containing 1 to 4 carbon atoms.

6. A therapeutic composition as claimed in claim 1 and in a unit dosage form containing from 10 to 150 mg. of 3-ethoxycarbonyl-5-methylpyrazole.

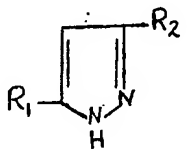
7. A therapeutic composition as claimed in claim 1 and in a unit dosage form containing from 2.5 to 200 mg. of 3-carbamoyl-5-alkylpyrazole, said alkyl group containing 1 to 4 carbon atoms.

8. A therapeutic composition as claimed in claim 1 and in a unit dosage form containing from 10 to 150 mg. of 3-carbamoyl-5-methylpyrazole.

9. A therapeutic composition as claimed in claim 1 and in a unit dosage form containing from 2.5 to 200 mg. of 3-alkyl-monosubstituted carbamoyl-5-alkylpyrazole, said alkyl groups containing 1 to 4 carbon atoms.

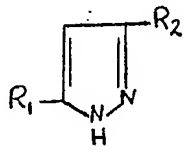
10. A therapeutic composition as claimed in claim 1 and in a unit dosage form containing from 10 to 150 mg. of 3-methylcarbamoyl-5-methylpyrazole.

11. A therapeutic composition as claimed in claim 1 comprising as the active ingredient a 3,5-disubstituted pyrazole having the general formula:—



wherein R_1 is alkyl and R_2 is a carboxyl, alkoxycarbonyl, carbamoyl or alkyl-monosubstituted carbamoyl the said alkyl group containing from 1 to 4 carbon atoms inclusive or a physiologically acceptable salt thereof, substantially as herein described with reference to any of the Examples.

12. A process for the preparation of a therapeutic composition as claimed in claim 1 comprising as the active ingredient a 3,5-disubstituted pyrazole having the general formula:—



wherein R_1 is alkyl and R_2 is a carboxyl, alkoxycarbonyl, carbamoyl or alkyl-monosubstituted carbamoyl, the said alkyl group containing from 1 to 4 carbon atoms inclusive, or a physiologically acceptable salt thereof, substantially as herein described with reference to any one of the Examples.

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Leamington Spa: Printed for Her Majesty's Stationery Office, by the Courier Press (Leamington) Ltd.—1966. Published by The Patent Office, 25 Southampton Buildings, London, W.C.2, from which copies may be obtained.